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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/644,288 | 08/20/2003 | Paul Diamond | PT100-3 | 5798 |

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| EXAMINER | |
|---|---|
| POPA, ILEANA | |
| ART UNIT | PAPER NUMBER |
| 1633 | |
| MAIL DATE | DELIVERY MODE |
| 05/02/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/644,288 | DIAMOND, PAUL | |
| | Examiner | Art Unit | |
| | Ileana Popa | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-16,21,26,28,31 and 33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20,22,24,25,27,29,30,32 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/29/2007 has been entered.

2. Claims 1-16, 21, 26, 28, 31, and 33-35 have been withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim. Claims 37 and 38 are new.

Claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36-38 are under examination

### *Claim Rejections - 35 USC § 112, enablement*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 remain and the new claims 37 and 28 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement for the reasons of record set forth in the prior Office Actions.

Applicant argues that the passage of Sledz et al. originally cited for delivery concerns in the non-final Office action of 02/13/2006 specifically relates to stability in circulation *in vivo* and this concern does not apply to plants. Applicant submits that methods for efficient inducing gene silencing in plants are well known in the art and requests that the Examiner provides an indication that the claimed invention is enabled for plants and other specific organisms. With respect to silencing in animals, Applicant submits that *in vivo* silencing in animals such as mice and *Drosophila* was also well known in the art and even Woessmann et al. cited by the Examiner teach that effective siRNAs are usually identified at high frequency in cultured cells and in mice. Applicant argues that nonspecific effects are not necessarily a problem as long as the desired specific effect is obtained, especially that the claimed invention does not cover genetically engineered human beings. With respect to Woessmann et al., Applicant argues that the reference teaches tumor cells and oncogenes, wherein tumor cells exhibit hypermutability, whereas the present invention involves RNA silencing of a preselected repressor protein linked to a recombinase gene expression element and therefore is totally different from the situation of silencing oncogenes in tumor cells. With respect to Opalinska et al., Applicant submits that there are substantial differences between antisense oligonucelotides and RNA silencing and therefore the Examiner's conclusion that consideration that apply to antisense oligonucleotides also apply to siRNAs is not supported by specific technical reasons and ignores the art-recognized differences between conventional and antisense technology and RNA silencing technology. Applicant submits that the teachings of Opalinska et al. contradict the

teachings of Sledz et al., Woessmann et al., and the references cited by the Applicant that support the enablement of the claimed invention, as discussed above. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Although it is true that gene silencing is well documented in plants and can be achieved in animals in certain situations, the main problem is that the instant claims require a cell expressing a repressible promoter operably linked to a site specific recombinase and a gene encoding a repressor protein, wherein when the repressor protein is expressed it represses the repressible promoter and thus it represses the expression of the site specific recombinase. Applicant contemplates to use RNA silencing against the mRNA encoding the repressor protein to induce the repressible promoter to direct expression of the site specific recombinase in the cell, which site specific recombinase excises the preselected DNA from the cell genome. However, as noted in the non-final Office action of 02/13/2006, based on the teachings of the art, one of skill in the art would not readily recognize that silencing of a single repressor protein would necessarily result in the de-repression of the cognate promoter. The art clearly teaches that transcription is carried out by assemblies of transcription factors, and many of them are redundant in the cell. For example, Arnold et al. (Int J Dev Biol, 1966, 40: 345-353, Abstract, of record) studying the role of the four myogenic regulating genes during mouse embryogenesis have found that Myf-5 and MyoD individually are not essential for the skeletal muscle development because they have redundant function.

The specification does not provide any example of a repressible promoter/repressor protein pair that could be used in the present invention. The art does not provide this guidance. Therefore, one of skill in the art would not know what promoter/repressor pair to chose among the many existing possibilities. To practice the claimed invention, one of skill in the art would have to first determine how the transcription machinery assembles to each specific promoter, the transcription factors that are part of that machinery, and which transcription factors are redundant. It is noted that this is not routine experimentation. It is also noted that the same promoter can be active in one cell type and inactive in another cell type, depending on what transcription factors assemble at the promoter in a particular cell type. The data above is known only for a few promoters in a few cells, and therefore, one of skill in the art would require undue experimentation to accumulate the necessary knowledge to practice the invention with any promoter, in any cell (*in vitro* or *in vivo*) *or* organism. Importantly, Applicant did not address this issue. This is compounded by the teachings of Sledz et al., Opalinska et al., and the other references cited by the Examiner in the non-final Office action of 02/13/2006. It is noted that Applicant's arguments regarding Woessmann et al. are found persuasive. However, the teachings of Sledz et al. and Opalinska et al. are still applied as set forth in the non-final Office action of 02/13/2006. Although the teachings of Sledz et al. do not apply to plants, beside plants and cells in culture, the claims are broadly drawn to any animal. With respect to Opalinska et al., Applicant did not provide any evidence that their teachings cannot be also applied to siRNAs. Applicant's arguments cannot replace evidence when evidence is necessary. The argument that

the antisense oligonucleotide and siRNAs act via entirely different mechanisms is not found persuasive because the citation from Opalinska et al. does not refer to this. The citation refers to problems such as *in vivo* delivery to a cell, which has nothing to do with the mechanism of action, which comes into effect after the antisense oligonucleotides or siRNAs are delivered to the cell and reach their target inside the cell. The art clearly teaches that the same problems apply to siRNAs (which are oligonucleotides), i.e., problems with the delivery to and inside a desired cell such that they reach their intracellular target. Therefore, even if, in certain situation, silencing in animals can take place, this is still unpredictable (see Sledz et al. and Opalinska et al.), which adds to the main problem discussed above. For all these reasons, the rejection is maintained.

## *New Rejections*

### *Claim Rejections - 35 USC § 101*

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 18, 19, 22, 24, 29, 30, and 32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The term "cell not integrated with a human being" is not defined by the specification and in fact the cell could be present in a human being and not integrated (i.e., blood cells) or the cell could be transplanted into a human being and not become integrated with the human being (i.e., transplanted blood cells, for example); however the nonintegrated cells are still part

of a human being. The scope of the claims, therefore, encompasses a human being and human beings are non-statutory subject matter.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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